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Type 2 Diabetes, Mitochondrial Biology and the Heart

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Abstract

Diabetes is recognized as an independent risk factor for cardiovascular morbidity and mortality. This is due, in large part, to premature atherosclerosis, enhanced thrombogenicity and activation of systemic inflammatory programs with resultant vascular dysfunction. More enigmatic mechanisms underpinning diabetes-associated cardiac pathophysiology include the direct metabolic consequences of this disease on the myocardium. Nevertheless, a role for diabetes-associated disruption in cardiac contractile mechanics and in increasing cardiomyocyte susceptibility to ischemic-stress has been implicated independent of vascular pathology. This review will focus broadly on the direct effects of diabetes on the cardiac myocardium with more specific reference to the role of the modulation of cardiomyocyte mitochondrial function in these disease processes. This focus in part, stems from the growing recognition that in some instances mitochondrial dysfunction is central to the development of insulin resistance and diabetes, and in others, diabetes associated disruption in mitochondrial function exacerbates and accentuates the pathophysiology of diabetes.

Keywords

Mitochondria; Diabetic cardiomyopathy; Type 2 diabetes; Db/db; Ob/ob

1. Introduction

Type 2 diabetes mellitus (T2DM) in combination with obesity are the fastest growing risk factors that adversely effect cardiovascular disease incidence and outcomes [1,2]. These diabetes associated cardiac complications are due, in large part, to perturbed cholesterol, vascular and platelet biology. The pathophysiology of these effects in T2DM have been extensively reviewed [3–5] and are not the focus of this manuscript. Interestingly, the effect of T2DM on the myocardium is not as well characterized. However, it is recognized that with T2DM the myocardium is predisposed to cardiac mechanical dysfunction and to diminished myocardial tolerance to biological stressors [6].

T2DM is associated with insulin resistance and a relative defect in pancreatic β -cell functioning that leads to reduced insulin mediated glucose uptake, increased hepatic glucose production and impaired suppression of lipolysis. These changes in turn alter the metabolic milieu within which the heart functions. The consequences and mechanistic interplay between T2DM, mitochondrial energetics and the heart form the core of this review.

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The heart is voracious in its appetite for energy, to such an extent that it generates and consumes a mass of ATP daily that surpasses cardiac mass itself by approximately 5–10 fold [7]. This unrelenting demand for energy reflects the continuous contractile functioning of the heart to sustain systemic circulation and nutrient supply. This high energy flux translates into the cardiomyocyte having a mitochondrial volume between 23% and 32% of myocellular volume {Schaper, 1985 #3356}. Interestingly, cardiac mitochondrial density increases from man to mouse in parallel with increasing heart rate and oxygen consumption {Schaper, 1985 #3356}. Disruption of mitochondria in other tissues are a *sine qua non* of established type 2 diabetes mellitus (T2DM) [9,10]. Hence, by employing ‘Occam’s Razor’ a reductionist hypothesis can be proposed that ‘cardiac function will be perturbed in T2DM due to mitochondrial dysfunction’. However, the biological relationship between T2DM, mitochondria and cardiac function is not straight forward and this manuscript is tasked to explore the current data supporting a more complex hypothesis regarding the role of the mitochondrion in cardiac adaptation to T2DM and to furthermore evaluate whether the modulation of mitochondria may have utility in treating T2DM associated cardiovascular disease. For the purposes of this review the term diabetes will refer to T2DM and data from primary pancreatic β -cell destruction with resultant type 1 diabetes and the cardiac sequelae of this is not discussed.

2. Mitochondrial biology in the heart

Prior to exploring the changes in cardiac mitochondria in diabetes a brief overview of the regulation and control of mitochondria will be introduced with a focus on these programs in the heart.

2.1. Transcriptional control of mitochondrial homeostasis

The mitochondrial biogenesis regulatory program is defined as the inter-genomic control of mitochondrial dynamics, functional content and number required to maintain diverse homeostatic demands across tissue types (Reviewed [11,12]). In the heart, the prime mitochondria function is to facilitate oxidative phosphorylation for the generation of ATP [13]. Mitochondrial biogenesis requires coordinate regulation between the mitochondrial and nuclear genomes to coordinately encode and integrate ~77 proteins’ into multi-subunit complexes of the respiratory apparatus and for other proteins necessary for homeostatic mitochondrial functions (e.g. oxidative metabolism, reactive oxygen species (ROS) generation, utilization and breakdown and in intracellular calcium homeostasis). The molecular conductors of inter-genomic regulation of mitochondrial biogenesis and the electron transfer chain complex proteins include the nuclear regulatory proteins - nuclear respiratory factors (NRF) 1 and 2, the cyclic AMP response element binding protein (CREB) and transcription factor A of mitochondria (TFAM) [14–16]. Upstream, the transcriptional coactivator peroxisome proliferators activated receptor gamma coactivator 1 alpha and beta (PGC1’s) and the PGC1 related coactivator (PRC) modulate these nuclear regulatory proteins to subsequently activate target genes encoding regulatory enzymes of oxidative phosphorylation [17–19] and genes that modulate anti-oxidant defenses, including nuclear-encoded mitochondrial anti-oxidant enzymes and the uncoupling proteins [20,21].

The transcriptional regulatory control of mitochondria content and number in the heart is tightly controlled. Unfettered overexpression of PGC1 α in the murine heart results in a progressive and uncontrolled increase in mitochondrial number with resultant disruption in cardiomyocyte sarcomeric structure and myocardial contractile function [22]. Conversely, the genetic deletion of PGC-1 α results in diminished cardiac mitochondrial enzyme activities, diminished ATP production, blunted cardiac postnatal growth, diminished chronotropic capacity and an inability to appropriately augment cardiac workload in response to exercise or to β -adrenergic stimulation {Leone, 2005 #2980}[23]. Interestingly and in contrast, cardiac restricted overexpression of TFAM has no obvious cardiac basal phenotype and shows diminished

mortality in response to cardiac ischemia with reduced adverse remodeling and diminished oxidative stress [24]. In primary cardiomyocytes TFAM overexpression prevents elevated glucose mediated oxidative stress and mitochondrial bioenergetic deficits {Suarez, 2008 #3467}.

The genetic induction of the peroxisome proliferators activated receptor alpha (PPAR α), a transcriptional mediator of mitochondrial metabolic function, most closely resembles perturbations associated with diabetic heart disease {Finck, 2002 #1324}. The cardiac restricted upregulation of this transcription factor upregulates mitochondrial fatty acid β -oxidation (FAO) in parallel with a reduction in glucose uptake and oxidation {Finck, 2002 #1324; Park, 2005 #3247}. Interestingly, the concurrent uptake and storage of fat in the myocardium in these mice exceeds the rate of FAO, resulting in a cardiomyopathy, reminiscent of 'diabetic cardiomyopathy' {Finck, 2002 #1324; Finck, 2003 #3361}. The concept that excess uptake of fat itself predisposes to cardiomyopathy is shown in mice with cardiac restricted overexpression of lipoprotein lipase, PPAR γ and acyl CoA synthetase {Yagyu, 2003 #3456; Son, 2007 #3458; Chiu, 2001 #3473}.

Substrate selection and utilization is also perturbed in T2DM with diminished glucose metabolism as discussed below. From a regulatory perspective these changes are also under transcriptional control. In the heart and skeletal muscle T2DM and starvation concordantly upregulate PGC-1 α and PPAR α , which in turn upregulate pyruvate dependent kinase 4 (PDK4), a negative regulator of glucose oxidation, {Wu, 1998 #3465; Wu, 1999 #3464}. Inversely, in response to hypoxia, an environmental cue that enhances glucose utilization, cardiac PPAR α and PDK4 are downregulated {Razeghi, 2001 #1404}.

2.2. Post-translational regulatory control of mitochondrial function

The biochemical/hormonal modulators of the mitochondrial biogenic regulatory program are not restricted to, but include ROS, nitric oxide, hypoxia, calcium signaling, AMP levels and thyroid hormones [25–29]. The complex interplay between the molecular and biochemical mediators is epitomized by nitric oxide which not only upregulates mitochondrial biogenesis [30], but concurrently modulates oxidative phosphorylation through competitive inhibition of respiratory chain electron transfer [31,32]. Substrate availability to the heart also alters mitochondrial metabolism, and the elevation in circulating free fatty acids, evident in T2DM, has also been shown to decrease glucose oxidation via inhibition of pyruvate dehydrogenase as described by Randle {Randle, 1963 #818; Randle, 1998 #819}. Finally, in cardiomyocytes elevated glucose itself promotes O-linked β -N-acetylglucosamineglycosylation of mitochondrial electron transfer chain proteins resulting in impaired mitochondrial oxidative capacity {Hu, 2009 #3468}.

2.3. Fuel-substrate changes with T2DM and effects on cardiac mitochondria

T2DM is a continuum that in its earliest stages is accompanied by peripheral organ insulin resistance manifesting as a requirement for greater insulin concentrations to activate the insulin signaling pathway to facilitate glucose uptake and/or to inhibit gluconeogenesis. The most consequential organs with respect to glucose uptake, storage and redistribution and therefore the major peripheral organs modulating this progressive pathophysiology include skeletal muscle, adipose tissue and the liver. Although hyperinsulinemia might maintain glucose homeostasis, relative pancreatic β -cell dysfunction ultimately leads to elevated circulating levels of glucose. Moreover, insulin resistance in adipose tissue is associated with elevated circulating free fatty acids, which in concert with hepatic insulin resistance leads to hypertriglyceridemia [39] [40]. In skeletal muscle exposure to elevated glucose and free fatty acids results in mitochondrial injury and dysfunction [41].

The characterization of insulin resistance and its interrelationship to the mitochondria in the heart has been less well explored. It is of interest to note that in human diabetic subjects, at least prior to overt cardiovascular disease, cardiac glucose uptake in response to insulin is preserved despite increased insulin resistance in other peripheral tissues {Jagasia, 2001 #3357}. The assessment of insulin resistance in the heart of diabetic mice have also been explored. Db/db mice, which have defective leptin receptors, develop severe hyperglycemia in concert with hyperinsulinemia and elevated circulating free fatty acids levels are studied as a model system to evaluate systemic effects of T2DM. The ex-vivo assessment of cardiac insulin responsiveness in these mice show preservation of insulin sensitivity in the presence of low levels of glucose and fat in the perfusate {Hafstad, 2006 #3360}. However, insulin-resistance develops when glucose and fat concentrations are increased in the perfusate {Hafstad, 2006 #3360}. The effects of elevated fatty acids on cardiac insulin resistance is also evident in mice deficient in skeletal muscle lipoprotein lipase [42]. In these mice, marked elevation of circulating fatty acids and triglycerides in response to a high fat diet promote cardiac insulin resistance [42]. To date mitochondrial biology has not specifically been studied in these mice. Moreover, ob/ob mice which are leptin deficient, obese and display insulin resistance with euglycemia with concomitant disruption in circulating glucose and fatty acids exhibit diminished cardiac glucose oxidation, increased mitochondrial FAO and increased myocardial mitochondrial oxygen consumption [43,44]. These perturbations result in diminished mitochondrial efficiency (uncoupling) and result in a reduced capacity to respond to increased cardiac work-load [45]. The mechanism orchestrating this are proposed to result from the increased delivery of reducing equivalents by the enhanced mitochondrial fatty acid β -oxidation to a relatively downregulated electron transport chain resulting in increased ROS production, lipid peroxidation and oxidative stress [45,46]. In support of this observation mitochondrial integrity has been shown to be disrupted and electron transfer chain enzyme levels diminished in insulin resistant hearts in aging dogs compared to younger activity-matched controls [47]. The role of fatty acid uptake in propagating insulin resistance in the heart is further supported whereby the reduction in cardiac fatty acid uptake by the genetic depletion of the fatty acid transporter CD36, rescues the insulin resistant phenotype evident in cardiac restricted PPAR α transgenic mice [48].

Interestingly, despite the development of cardiac mitochondrial dysfunction with diabetes, these hearts do preferentially oxidize fatty acids. It has recently been shown that insulin resistance drives the cardiac mitochondrial biogenesis regulatory program via PPAR α [49]. This response is proposed to result from the increased PPAR α activation due to increased fat uptake and oxidation [50]. Although the cardiac mitochondrial number and content is increased in the insulin-resistant uncoupling protein-diphtheria toxin A transgenic mice, mitochondrial efficiency is diminished compared to controls and probably reflects, and is consistent with incomplete adaptation to these diabetes associated metabolic perturbations [49,51].

A potential deficit in studies investigating cardiac substrate preferences and utilization in the ex-vivo diabetic heart is the absence of ketone bodies in the perfusate. In-vivo and ex-vivo studies in multiple species show that the exposure of the myocardium to ketone bodies results in a relative reduction in the rate of FAO {Stanley, 2003 #3460;Stowe, 2006 #3461;Hasselbaink, 2003 #3462}. Although ketone metabolite levels are usually not present in high abundance in well controlled diabetes, elevation of levels does occur under poor diabetic control.

From a mitochondrial oxidative capacity perspective, the primary disruption of mitochondrial function in liver, skeletal muscle and adipocytes can promote the development of insulin resistance [52–54]. Whether primary mitochondrial defects are operational in cardiac insulin resistance does not appear to have been directly investigated. However, in the heart, the molecular disruption in insulin signaling following cardiac restricted depletion of insulin

receptors results in age-dependent impairment in mitochondrial oxidative phosphorylation capacity and augmentation in oxidative stress [Boudina, 2009 #3469].

3. Diabetes associated diseases of the myocardium and mitochondria

Although, the concept of diabetic cardiomyopathy has been part of the discourse for the past 35 years [56], the distinct clinical delineation of this condition from other cardiac comorbidities such as cholesterol mediated effects on vascular function (endothelial function, atherosclerosis and coronary artery disease) or from hypertension and associated cardiac hypertrophy is usually not practical. Nevertheless, clinical data is being accumulated that diabetes does impair cardiac function and ischemic tolerance, independent of other cardiac risk factors [1,57,58]. In this section we review the evidence whereby diabetes directly perturbs cardiac relaxation, contractile function and ischemic tolerance and explore this pathophysiology with the specific reference to mitochondrial biology. Additional mechanisms operational in diabetic cardiomyopathy include perturbations in calcium regulation and homeostasis and direct effects of disrupted insulin signaling. These additional biological pathways have recently been reviewed [6,59,60] and are not discussed further.

3.1. Diastolic and systolic heart failure in diabetes

Diastolic dysfunction is classically defined as abnormalities in the relaxation phase of the cardiac mechanical cycle, that delays ventricular filling and results in symptoms and signs of heart failure [Galderisi, 2006 #3466][61]. This was initially proposed to occur independently of systolic contractile dysfunction. However, with advancing cardiac imaging and hemodynamic measurements it is now recognized that a relative degree of contractile dysfunction accompanies filling/relaxation deficits in the majority of subjects [61]. As these concurrent perturbations in relaxation and contraction do not fit the classic clinical definition of systolic heart failure (a low ejection fraction), this clinical entity is now defined as heart failure with preserved ejection fraction [61]. In subjects with diabetes, this distinction may be academic, rather reflecting a continuum where the early deficit manifests as abnormal cardiac relaxation with progression to combined systolic and diastolic dysfunction [62]. Studying endomyocardial biopsy specimens Paulus and colleagues show that diabetic heart failure subjects with preserved ejection fraction have increased cardiomyocyte resting tension which is compatible with increased diastolic stiffness [62]. Furthermore, an increase in myocardial advanced glycation end products and collagen deposition were only observed in diabetic subjects following the onset of systolic dysfunction [62]. Whether this increased diastolic stiffness is related to mitochondrial defects in human subjects has not been directly investigated. However, it has been shown using ¹H-MRS that subjects with diabetes or glucose intolerance have increased cardiac steatosis [63], which may indirectly reflect diminished mitochondrial metabolic capacity. The measurement of high-energy phosphates in diabetic and non-diabetic subjects without clinical coronary artery disease and normal echocardiographic studies indirectly suggest that diabetic subjects have diminished cardiac energetics [64]. This study does not, however, directly implicate a mitochondrial deficit as aberrations in the creatine-kinase shuttle or creatine levels could also modulate these NMR spectra.

T2DM is known to enhance susceptibility to ischemic cardiomyopathy [Haffner, 1998 #3459], however, and paradoxically the additional pathology of T2DM in subjects with non-ischemic cardiomyopathy appears to confer a survival advantage [De Groote, 2004 #3354]. This finding was similarly found in a smaller cohort of T2DM subjects where heart failure survival was inversely correlated with blood sugar control as measured by HbA1c [Eshaghian, 2006 #3355]. These findings are not uniform, in that other clinical studies globally show a worse outcome in systolic heart failure subjects with T2DM versus non-diabetic controls. A distinction between ischemia and non-ischemic cardiomyopathy may be operational in these conflicting findings, although the mechanisms governing these effects has to date not been elucidated.

The cardiac hemodynamic functioning of db/db mice have been directly assessed using an isolated working heart model system and show classical features of diastolic dysfunction as measured by an increased in the left ventricular end diastolic pressure and increased myocardial stiffness [65]. These perturbations are proposed to result from the diminution in myocardial efficiency as measured by the ratio between cardiac output (work) and oxygen consumed (MVO_2). This excess in MVO_2 was found to be exacerbated with higher levels of fat substrate for cardiac metabolism. Interestingly, in this study the stroke volume of the db/db mice were similar to the db/+ controls. Severson and colleagues show in similarly aged mice that diastolic and systolic perturbations are evident as measured in-vivo by echocardiography [66]. Furthermore, the db/db mice show diminished glucose uptake and an early thickening of the myocardium in young mice, with progressive systolic dysfunction with aging when measured in vivo using PET and MRI imaging [67]. The metabolic underpinning of these deficits is further supported in that overexpression of the glucose transporter GLUT4 with concomitant increase in glucose oxidation rescues cardiac contractile function in db/db mice [66,68].

At 11 weeks of age, ob/ob mice demonstrate increase neutral lipid accumulation in the heart with echocardiographic parameters consistent with diastolic dysfunction [69]. Furthermore, Abel and colleagues demonstrate that these mice have impaired mitochondrial respiratory capacity in association with diminished pyruvate dehydrogenase activity and a restricted glucose-dependent oxidative capacity response to increased workload [45]. In response to the addition of fat substrate, oxygen consumption is enhanced, but at the expense of cardiac efficiency suggesting that these mitochondria are susceptible to fat-mediated mitochondrial uncoupling [45]. Indeed direct measurement of mitochondrial proton leak in db/db mice supports the existence of fatty acid induced mitochondrial uncoupling {Boudina, 2007 #3470}.

Additional animal models that support these concepts include the Otsuka Long-Evans Tokushima Fatty rats which show disrupted left ventricular diastolic filling [70] and evidence that cardiac contractile dysfunction is accelerated and mortality increased in hypertensive rats when they are subject to a high sugar-diet [71]. Moreover, high-fat feeding to Wistar rats also evokes cardiac contractile dysfunction, which appears to result from enhanced fatty acid uptake through CD36 and intramyocellular triacylglycerol accumulation {Ouwens, 2007 #3471}.

3.2. Diabetes and cardiac ischemia-tolerance

As mitochondrial biology is increasingly being recognized as a pivotal organelle in the modulation of cardiac ischemia tolerance [72,73], perturbations in cardiac mitochondrial metabolism associated with T2DM may be expected to attenuate myocardial tolerance to ischemia. In humans, this is supported in that following myocardial-infarction, the incidence of heart failure is increased in diabetic subjects far in excess of non-diabetic subjects with similar infarct sizes [74,75].

Interestingly, db/db mice also show increased susceptibility to cardiac ischemia as measured by post-ischemic recovery of contractile function [76,77] in parallel with a diminished capacity to utilize glucose in this oxygen-deficient milieu [77]. This increased susceptibility to ischemic injury in db/db mice also results in a greater incidence of heart failure and enhanced mortality in response to chronic ischemia [78]. In parallel, cardiac contractility and survival are diminished in ob/ob mice following chronic myocardial ischemia [79] and following diet-induced obesity in wildtype mice [80].

4. Therapeutic modulation of mitochondria in diabetes and the effects on cardiac function

As the regulatory control of mitochondrial bioenergetics are being identified, therapeutic agents directed at modulating mitochondrial function in the heart are being developed and tested [81]. The most promising mitochondrial and metabolic modulatory compounds that may improve diabetic cardiac function and/or stress tolerance include the PPAR γ , the PPAR δ and SIRT1 agonists. Moreover, in light of increased oxidative stress in T2DM {Boudina, 2007 #3470;Boudina, 2009 #3469}, strategies to combat this in the diabetic heart are also briefly reviewed.

4.1. PPAR γ agonists

Thiazolidinediones are part of the therapeutic armamentarium in the management of T2DM. Interestingly, they directly upregulate mitochondrial biogenesis in adipose tissue and in skeletal muscle [53,82]. This effect has not been shown in the heart which probably reflects lower expression of PPAR γ in the heart. Interestingly though the thiazolidinedione rosiglitazone does improve myocardial efficiency by diminishing the augmented MVO₂ in db/db mice [83]. This is thought to occur in part by normalizing plasma glucose and fatty acid levels [83] and in restoring cardiac substrate utilization and insulin signaling [83,84]. As may be expected these metabolic changes also improve cardiac ischemia-tolerance [83,84]. Caveats regarding the utilization of thiazolidinediones for cardiovascular disease include that these ischemia-protective effects do not appear to extend to the non-diabetic heart [85] and that the composite of cardiac effects of the thiazolidinedione class of compounds is being questioned in light of a possible enhanced risk of acute coronary syndromes in humans [86]. Moreover, as insulin signaling modulates cardiac growth, Abel and colleagues directly investigated the effects of non-thiazolidinedione PPAR γ agonists on cardiac hypertrophy. PPAR γ -agonist therapy resulted in increased cardiac volume with ventricular hypertrophy in wildtype mice and in mice with cardiac restricted knockout of the insulin receptor {Sena, 2007 #3474}. These effects are thought to occur due to the plasma volume expansion effects of PPAR γ activation, and may impose an additional impediment for the use of PPAR γ agonist therapy in subjects with diabetes associated cardiac dysfunction. This limitation is also evident in the clinical arena {Waksman, 2008 #3487}.

4.2. PPAR δ agonists

Cardiac restricted overexpression of PPAR δ does not alter the rate of fatty acid uptake nor oxidation but does increase glucose uptake and oxidation {Burkart, 2007 #3475}. This metabolic profile would be expected to facilitate glucose utilization and thereby potentially ameliorate the development of insulin resistance or T2DM. In light of this desirable metabolic profile investigators have studied the systemic insulin-sensitizing effects of the PPAR δ agonist GW501516 {Oliver, 2001 #3416}. In wildtype mice placed on a high-fat diet, a 2 month treatment period with GW501516 resulted in reduction in weight gain, increased type 1 skeletal muscle fiber type and improve glucose tolerance compared to vehicle treated controls {Wang, 2004 #3414}. A recent proof of concept study in human subjects showed that a two-week treatment of insulin resistant subjects with GW501516 did improve insulin sensitivity {Riserus, 2008 #3432}. Although the cardiac effects of GW501516 have not been directly explored in the context of diabetogenic stressors, in cardiac derived H9c2 myoblasts, the PPAR δ agonist is protective against oxidative stress {Pesant, 2006 #3476}. This class of agents requires additional investigation, but may be an interesting compound to treat diabetes in general and possibly directed against diabetes associated cardiac metabolic perturbations.

4.3. Sirtuin activators

The plant-derived polyphenol resveratrol (3,5,4'-trihydroxystilbene) is enriched in red wine and functions as a caloric restriction mimetic via upregulation of SIRT1 and AMP-activated kinase (AMPK) [87–89]. Additionally it exhibits antioxidant properties [90] and upregulates the mitochondrial biogenesis program [87]. Consistent with its known pleiotropic effects resveratrol administration confers protection against cardiac ischemia-reperfusion injury [90–92] although this has not been directly investigated in T2DM diabetic models. To differentiate the cardioprotective properties from the pleiotropic effects of resveratrol, small molecules that directly activate SIRT1 are being investigated [93]. Recently identified SIRT1 activators do prevent the onset of T2DM [94] and promote fatty acid oxidation and mitochondrial function [95]. Whether these SIRT1 activators can directly ameliorate cardiac stress-tolerance and the adverse diabetic effects on cardiac mitochondria need to be investigated.

4.4 Antioxidant therapy

Evidence supports excess ROS generation in parallel with mitochondrial dysfunction in the diabetic heart {Boudina, 2007 #2889;Boudina, 2009 #3469}. This excess ROS is proposed to contribute to both functional perturbations and susceptibility to ischemic injury in the diabetic heart. Contractile function has been studied in primary cardiomyocytes extracted from the T2DM-like agouti mouse with or without overexpression of catalase {Ye, 2004 #3481}. The presence of this ROS detoxifying enzyme enhanced ex-vivo contractile function of agouti mouse cardiomyocytes {Ye, 2004 #3481}. In this regard whether resveratrol-like compounds or PPAR δ agonists could have protective effects targeting ROS in the diabetic heart would be of considerable interest.

5. Limitations of murine models of T2DM

The circulating metabolic perturbations, including elevations in glucose, fat and insulin levels that associate with the development of insulin resistance and T2DM are usually chronic, dynamic and moderate compared to normal control subjects. The mouse and dietary models employed to study T2DM are invariably 'all or nothing' modulations employing transgenic and knockout mice and extreme dietary manipulations. Although these models can give us insight at the extremes of the metabolic profile and assist in the dissection of the interaction between e.g. regulatory programs and metabolism and metabolites and mitochondrial function, it is important to appreciate these limitations and to translate these findings to the patient to formulate the pathophysiologic framework of the interplay between T2DM, mitochondria and cardiac function.

6. Conclusions

The weight of the evidence strongly suggests that the mitochondrial perturbations identified in the diabetic heart are secondary to the systemic effects of T2DM. This hypothesis is schematized in figure 1 and described here. In brief, the major T2DM associated systemic metabolic perturbations including elevated circulating free-fatty acids and hyperglycemia appears to provoke cardiac mitochondrial dysfunction and regulatory changes. Furthermore, the role of disrupted insulin signaling and hyperinsulinemia in this program may be 'operatives' in disrupting cardiac mitochondrial function. The direct effect of these T2DM metabolic consequences on the cardiac mitochondria require further investigation. Nevertheless, mitochondrial dysfunction identified in the 'diabetic heart' in concert with the additional cardiac deficits associated with T2DM probably contribute in tandem to disrupt cardiac contractile function and diminish cardiac stress-tolerance. As therapeutic options are being explored that modulate mitochondrial function, it will be intriguing to investigate whether

optimization of cardiac mitochondrial functioning may have ameliorative effects on the 'diabetic heart'.

Furthermore and with probable more immediate benefit, it has been well established that lifestyle interventions including weight loss and exercise can both delay the onset of diabetes and delay its progression {Orchard, 2005 #3177; Toledo, 2007 #3284; Li, 2008 #3178}. In light of the information from this review, modulating these environmental stressors may be expected to improve functioning in the diabetic heart by diminishing cardiac exposure to this nutrient overload. This concept has recently begun to be explored and an elegant study shows that robust weight loss in response to bariatric surgery not only has ameliorative effects on circulating glucose, insulin, free fatty acid and leptin levels, but also normalizes cardiac diastolic function {Leichman, 2008 #3485}.

Taken together, the studies reviewed implicate mitochondrial dysfunction in the pathophysiology of adverse cardiac effects of T2DM. Moreover, these data suggest that broad lifestyle modifications to attenuate adverse environmental cues and novel therapeutics to target mitochondrial biology may potentially have additive effects in the overall management of T2DM and in the protection of the heart.

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Abbreviations

CREB	cyclic AMP response element binding protein
MRI/MRS	magnetic resonance imaging/spectroscopy
NRF	nuclear respiratory factor
PET	positron emission tomography
PPAR	peroxisome proliferator activated receptor
PGC-1α	PPAR gamma associated coactivator – 1 alpha
ROS	reactive oxygen species
SIRT1	sirtuin family member 1
T2DM	type 2 diabetes mellitus

TFAM

transcription factor A of mitochondria

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Circulatory Metabolites in T2DM and Cardiac Mitochondrial Effects

Figure 1.

Schematic of interplay between plasma substrate alteration with diabetes and heart mitochondrial and cardiac functional responses. The initial cardiac exposure to elevated free fatty acids and glucose (1) may evoke cardiac mitochondrial ROS generation and result in oxidative damage to the mitochondria and cardiomyocytes in part via lipid peroxidation. The elevated exposure to fatty acids, in turn appears to activate the mitochondrial biogenesis program (2). Despite the increase in mitochondrial numbers, mitochondrial efficiency is diminished in the diabetic heart (3). This in turn, coupled to the reduced capacity to use glucose predisposes to both ischemia intolerance and to mechanical dysfunction (4).